Summary of Safety and Effectiveness

Original PMA P010012

CONTAK CD® CRT-D System

and

EASYTRAK® Coronary Venous Steroid-Eluting Single-Electrode Pace/Sense Lead, Models 4510, 4511, 4512, 4513

Summary of Safety and Effectiveness

1 GENERAL INFORMATION

Device Generic Name:	Cardiac Resynchonization Therapy Defibrillator (CRT-D) System
Device Trade Name:	Guidant CONTAK CD® CRT-D system including the: • CONTAK CD CRT-D pulse generator Model 1823 • Software Application Model 2848 (Version 3.1) EASYTRAK® Coronary Venous Steroid-Eluting Single Electrode Pace/Sense Lead, Models 4510, 4511, 4512, 4513 System accessories: • Finishing Wire, Models 6730, 6731, 6732, 6733 • Suture Sleeve, Model 6741 • LV®-1 Lead Cap, Model 6742 • LV®-1 Lead Port Plug, Model 6743 • Lead Adapter, Model 6744
Applicant's Name and Address:	GUIDANT Corporation, Cardiac Rhythm Management 4100 Hamline Avenue North St. Paul, Minnesota 55112-5798
PMA Number:	P010012
Preapproval Inspection	April 29, 2002
Date of Panel Recommendations	July 10, 2001
Date of Notice of Approval to Applicant	May 02, 2002

2 INDICATIONS FOR USE

2.1 CONTAK CD CRT-D SYSTEM

The CONTAK CD CRT-D System is indicated for use in the following:

Patients who are at high risk of sudden cardiac death due to ventricular arrhythmias and who have moderate to severe heart failure [New York Heart

Association (NYHA) Class III/IV] including left ventricular dysfunction (ejection fraction (EF) ≤ 35%) and QRS duration ≥120 ms and remain symptomatic despite stable, optimal heart failure drug therapy.

Patient populations at high risk of sudden cardiac death due to ventricular arrhythmias include, but are not limited to, those with:

- Survival of at least one episode of cardiac arrest (manifested by the loss of consciousness) due to a ventricular tachyarrhythmia.
- Recurrent, poorly tolerated sustained ventricular tachycardia (VT).

  NOTE: The clinical outcome of hemodynamically stable, sustained-VT patients is not fully known. Safety and effectiveness studies have not been conducted.

- Prior myocardial infarction, left ventricular ejection fraction of ≤35%, and a documented episode of nonsustained VT, with an inducible ventricular tachyarrhythmia. Patients suppressible with IV procainamide or an equivalent antiarrhythmic (drug) have not been studied.

2.2 EASYTRAK LEAD

The Guidant EASYTRAK coronary venous, steroid-eluting, single-electrode pace/sense leads, Models 4510/4511/4512/ 4513, are transvenous leads intended for chronic left ventricular pacing and sensing via the coronary veins when used in conjunction with a compatible Guidant cardiac resynchronization therapy (CRT) device that accepts the LV-1 connector.

3 SYSTEM DESCRIPTION

3.1 CONTAK CD CRT-D PULSE GENERATOR

The Guidant CONTAK CD CRT-D pulse generator, Model 1823, provides ventricular tachyarrhythmia and cardiac resynchronization therapies. Ventricular tachyarrhythmia therapy is for the treatment of VT and ventricular fibrillation (VF), rhythms that are associated with sudden cardiac death (SCD). Cardiac resynchronization therapy uses simultaneous biventricular electrical stimulation to synchronize ventricular contractions. The device uses accelerometer-based adaptive-rate bradycardia therapy similar to Guidant's commercially available VENTAK® family of implantable cardioverter defibrillators (ICDs). The pulse generator, an atrial lead, and two ventricular leads connected in parallel configuration constitute the implantable portion of the CRT-D

system. The pulse generator accepts one atrial lead (IS-1 connector type), one coronary venous lead (LV-1 connector type) (EASYTRAK®), and one cardioversion/ defibrillation lead (DF-1/IS-1 connector type).

Cardioversion/defibrillation therapies include a range of low- and high-energy shocks using either a biphasic or monophasic waveform. The CONTAK CD CRT-D pulse generator uses the Guidant TRIAD® electrode system for defibrillation energy delivery. By using the metallic housing of the pulse generator as an active electrode, combined with the Guidant ENDOTAK (approved in P910073) two-electrode defibrillation lead, energy is sent via a dual-current pathway from the distal shocking electrode to the proximal electrode and to the pulse generator case. The CONTAK CD CRT-D system also offers a variety of antitachycardia pacing (ATP) schemes to terminate slower, more stable ventricular tachyarrhythmias. Bradycardia pacing with resynchronization therapy, including adaptive-rate features, is available to detect and treat bradyarrhythmias and to support the cardiac rhythm after defibrillation therapy.

The ZOOM® Programming System, which includes the Model 2920 Programmer/ Recorder/ Monitor (PRM) (approved in P840068/S039, P910077/S031, P940031/S023, and P960040/S013), the Model 2848 Software Application (Version 3.1), and an accessory telemetry wand, constitutes the external portion of the CONTAK CD CRT-D system. The external components allow interrogation and programming of the pulse generator as well as access to the device's diagnostic features. The CONTAK CD CRT-D system can be programmed to provide a variety of therapy options. It also can provide noninvasive diagnostic testing and therapy history data.

3.2 EASYTRAK LEAD

The EASYTRAK coronary venous, steroid-eluting single-electrode pace/sense leads, Models 4510/4511/4512/4513, provide chronic pacing and sensing of the left ventricle. The lead is placed by inserting it through the coronary sinus and into a branch of the cardiac veins. The over-the-wire design has an open inner lumen which allows passage over a guide wire.

The lead features a single pacing electrode. Distal to the electrode is a drug collar with an anti-inflammatory glucocorticosteroid. The distal end of the lead has passive fixation tines, and the tip is constructed of soft silicone rubber.

The electrode is connected by a multifilar conductor coil to the terminal pin on the proximal end of the lead. The LV-1 terminal pin is hollow to allow for insertion of the guide wire and is streamlined to facilitate guide catheter removal. The LV-1 lead port in

the header of a compatible heart failure device has sealing rings that electrically insulate the terminal pin. The EASYTRAK lead is constructed of silicone rubber tubing, which electrically insulates the coil. Additionally, an abrasion-resistant polyurethane sleeve over the silicone insulation covers all but the terminal and distal-most portion of the lead body.

The EASYTRAK lead is used in conjunction with the CONTAK CD CRT-D Model 1823 pulse generator, or a compatible Guidant CRT device, that accepts the LV-1 connector.

Implant accessory devices are available for use with the EASYTRAK lead. Implant accessory devices include guiding catheters, guide wires, finishing wires, and balloon catheters that are labeled for use with the EASYTRAK lead.

4 CONTRAINDICATIONS

The CONTAK CD CRT-D system is contraindicated for use in the following:

- Patients whose ventricular tachyarrhythmias may have a reversible cause such as 1) digitalis intoxication, 2) electrolyte imbalance, 3) hypoxia, 4) sepsis, or
- Patients whose ventricular tachyarrhythmias may have a transient cause, such as 1) acute myocardial infarction, 2) electrocution, or 3) drowning.

5 WARNINGS AND PRECAUTIONS

See device labeling.

6 ADVERSE EVENTS

6.1 OBSERVED ADVERSE EVENTS

The VENTAK® CHF/CONTAK® CD/EASYTRAK® Biventricular Pacing Study (hereafter referred to as the CONTAK CD Study) was a prospective, randomized, controlled, multicenter, double-blind study conducted at 47 sites in the United States and enrolled a total of 581 patients. Of these, 57 patients initially underwent a thoracotomy procedure to receive the Guidant Model 1822 VENTAK CHF AICD; 7 patients underwent a repeat procedure to receive an EASYTRAK lead. An additional 510 patients initially underwent an implant procedure to receive the Model 1823 CONTAK CD CRT-D pulse generator along with the EASYTRAK (Models 4510/4511/4512/4513) coronary venous, single-electrode pace/sense lead for a total of 517 patients who underwent an EASYTRAK lead implant procedure. In 69 patients the EASYTRAK lead implant attempt was unsuccessful.

Table 1 provides information on all adverse events reported from implant through the randomization period in patients attempted or implanted with the EASYTRAK lead. During this period, a total of 765 events were reported in 310 patients. Of these, 155 were classified as complications, and 610 were classified as observations.

Table 1: Adverse Events Through the Randomization Period

(765 Events in 517 patients implanted or attempted with the EASYTRAK lead, 2559 total device months)

	# Of Events (# of pts)[a]	% Complic-ations (Patients)	Complications per 100 Device Months (Events)	% Observations (Patients)	Observatrions per 100 Device Months (Events)
Total Adverse Events	**765 (310)**	**23.4 (121)**	**6.0 (155)**	**51.8 (268)**	**23.5 (610)**
PG-Related Events					
Migration of device	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Pacemaker mediated tachycardia (PMT)	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Telemetry difficulty	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
LV Lead-Related Events					
Loss of capture	43 (41)	5.6 (29)	1.1 (29)	2.5 (13)	0.5 (14)
Inappropriate shock due to oversensing	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Insulation breach observed	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
Multiple counting[b]	31 (22)	1.0 (5)	0.2 (5)	3.9 (20)	1.0 (26)
Phrenic nerve/diaphragm stimulation	15 (15)	0.4 (2)	0.1 (2)	2.5 (13)	0.5 (13)
RA Lead-Related Events					
Loss of capture	6 (6)	1.0 (5)	0.2 (5)	0.2 (1)	0.0 (1)
Oversensing	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Undersensing	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
RV Lead-Related Events					
Loss of capture	10 (9)	0.6 (3)	0.1 (3)	1.2 (6)	0.3 (7)
Elevated DFTs	6 (6)	0.4 (2)	0.1 (2)	0.8 (4)	0.2 (4)
Inappropriate shock above rate cutoff	49 (38)	0.4 (2)	0.1 (2)	7.2 (37)	1.8 (47)
Inappropriate shock due to oversensing	5 (4)	0.0 (0)	0.0 (0)	0.8 (4)	0.2 (5)
Non-conversion of VF	1 (1)	0.2 (1)	0.0 (1)	0.0 (0)	0.0 (0)
Oversensing	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Phantom shock	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Phrenic nerve/diaphragm stimulation	5 (5)	0.4 (2)	0.1 (2)	0.6 (3)	0.1 (3)
Subtotal Device-Related Events	**186 (135)**	**9.5 (49)**	**2.1 (54)**	**19.0 (98)**	**5.1 (132)**
Procedure-Related Events					
AV Block	7 (7)	0.0 (0)	0.0 (0)	1.4 (7)	0.3 (7)
Coronary sinus dissection	5 (5)	0.0 (0)	0.0 (0)	1.0 (5)	0.2 (5)
Coronary venous perforation	5 (5)	0.2 (1)	0.0 (1)	0.8 (4)	0.2 (4)
Hematoma	11 (10)	0.8 (4)	0.2 (4)	1.2 (6)	0.3 (7)
Hypotension	7 (7)	0.0 (0)	0.0 (0)	1.4 (7)	0.3 (7)
Infect ion, post-operative wound	7 (7)	0.6 (3)	0.1 (3)	0.8 (4)	0.2 (4)
Pneumothorax	7 (7)	0.8 (4)	0.2 (4)	0.6 (3)	0.1 (3)
Post surgical wound discomfort	10 (9)	0.2 (1)	0.0 (1)	1.5 (8)	0.3 (9)
Renal failure	5 (5)	0.2 (1)	0.0 (1)	0.8 (4)	0.2 (4)
Other[c]	18 (18)	1.2 (6)	0.2 (6)	2.3 (12)	0.5 (12)
Subtotal Procedure Related Events	**79 (71)**	**3.9 (20)**	**0.7 (17)**	**10.0 (51)**	**2.2 (56)**
Cardiovascular Related Events					

	# Of Events (# of pts)[a]	% Complic-ations (Patients)	Complications per 100 Device Months (Events)	% Observations (Patients)	Observatrions per 100 Device Months (Events)
AV Block	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Arrhythmia - SVT	49 (42)	0.2 (1)	0.0 (1)	7.9 (41)	1.8 (48)
Arrhythmia - VT	20 (17)	1.0 (5)	0.2 (5)	2.7 (14)	0.6 (15)
Arrhythmia - brady	16 (14)	0.2 (1)	0.0 (1)	2.5 (13)	0.6 (15)
Cardiac arrest	2 (2)	0.4 (2)	0.1 (2)	0.0 (0)	0.0 (0)
Chest pain	30 (20)	1.0 (5)	0.2 (5)	3.1 (16)	1.0 (25)
Coagulopathy	3 (3)	0.2 (1)	0.0 (1)	0.4 (2)	0.1 (2)
Congestive heart failure	140 (91)	3.5 (18)	0.7 (18)	16.1 (83)	4.7 (122)
Distal thromboemboli	3 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (3)
Dizziness	17 (17)	0.0 (0)	0.0 (0)	3.3 (17)	0.7 (17)
Dyspnea (shortness of breath)	16 (13)	0.0 (0)	0.0 (0)	2.5 (13)	0.6 (16)
Fatigue	10 (10)	0.0 (0)	0.0 (0)	1.9 (10)	0.4 (10)
Hypertension	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Hypotension	11 (9)	0.2 (1)	0.0 (1)	1.7 (9)	0.4 (10)
Myocardial infarction	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Pacemaker syndrome	1 (1)	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (1)
Palpitations	2 (2)	0.0 (0)	0.0 (0)	0.4 (2)	0.1 (2)
Pulmonary edema	6 (6)	0.4 (2)	0.1 (2)	0.8 (4)	0.2 (4)
Shock	4 (4)	0.2 (1)	0.0 (1)	0.6 (3)	0.1 (3)
Stroke syndrome or CVA	4 (4)	0.0 (0)	0.0 (0)	0.8 (4)	0.2 (4)
Syncope	9 (9)	0.0 (0)	0.0 (0)	1.7 (9)	0.3 (9)
Thrombosis	3 (3)	0.0 (0)	0.0 (0)	0.6 (3)	0.1 (3)
Vascular related	6 (6)	1.0 (5)	0.2 (5)	0.2 (1)	0.0 (1)
Subtotal Cardiovascular Related Events	**358 (200)**	**7.7 (40)**	**1.6 (42)**	**35.6 (184)**	**12.2 (316)**
Total Non-cardiovascular Related Events	**142 (92)**	**6.2 (32)**	**1.5 (39)**	**13.5 (70)**	**4.0 (103)**

a. The total number of patients for a given event represents the unique number of patients who experienced that event. The total may not be equal to the sum of patients with complications or observations because some patients experienced more than one event that fell into both categories.

b. Sensing of two ventricular intrinsic events when only one intrinsic event is present due to intraventricular conduction delay.

c. Other procedure related events occurred in three patients or fewer: Guide wire fracture (1), Hemorrhage (3), Finishing wire left in lead (1), Non-conversion of VF (1), Perforation, arterial (1), Perforation, cardiac (1), Perforation, venous (2), Pericardial effusion (3), Pericarditis (1), Physiological reaction (1).

A total of 109 deaths occurred during the study. These deaths occurred during the study periods as shown in Table 2 along with the cause of death as adjudicated by an independent events committee.

Table 2: Deaths that Occurred During the Study

All patients enrolled, N=581

		Cause of Death				
Study Period	**# of pt deaths**	**Cardiac: Pump Failure**	**Cardiac: Arrhythmic**	**Cardiac: Other**	**Non-Cardiac**	**Unknown**
After unsuccessful implant procedure	2	1	1	0	0	0
Peri-operative (<= 30 days)	10	5	2	0	2	1
Randomized therapy phase*: No CRT	16	9	0	1	3	3
Randomized therapy phase*: CRT	11	4	1	2	2	2
Post -randomized therapy phase**	70	28	5	1	16	20
Total	**109**	**47**	**9**	**4**	**23**	**26**

* Day 31 to 120 for Phase I patients, day 31 to 210 for Phase II patients

** Day 121 and beyond for Phase I patients, day 211 and beyond for Phase II patients

6.2 POSSIBLE ADVERSE EVENTS

Based on the literature and ICD implant experience, the following alphabetical list includes possible adverse events associated with implantation of an ICD system:

- Acceleration of arrhythmias
- Air embolism
- Allergic reaction
- Bleeding
- Cardiac tamponade
- Chronic nerve damage
- Conductor coil fracture
- Death
- Elevated thresholds
- Erosion/extrusion
- Extracardiac stimulation (e.g., phrenic, diaphragm, chest wall)
- Fibrotic tissue formation (e.g., keloid formation)
- Fluid accumulation
- Formation of hematomas or cysts
- Heart block
- Inability to defibrillate or pace
- Inappropriate therapy (e.g., shocks, ATP, pacing)
- Incomplete lead connection with pulse generator
- Infection
- Lead displacement/dislodgment
- Lead insulation breakage or abrasion
- Lead tip deformation and/or breakage
- Local tissue reaction
- Muscle and nerve stimulation
- Myocardial trauma (e.g., cardiac perforation, irritability, injury)
- Myopotential sensing
- Oversensing/undersensing
- Pacemaker mediated tachcardia
- Pericardial rub, effusion
- Pneumothorax
- Random component failures
- Shunting current or insulating myocardium during defibrillation with intemal or external paddles
- Thrombosis/thromboemboli
- Valve damage
- Venous occlusion
- Venous trauma (e.g., perforation, dissection, erosion)

Patients susceptible to frequent shocks despite antiarrhythmic medical management may develop psychological intolerance to an implantable system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking

In addition to the implantation of an ICD system, possible adverse events associated with implantation of a coronary venous lead system are listed below in alphabetical order:

- Allergic reaction to contrast media
- Breakage/failure of implant tools
- Coronary venous occlusion
- Coronary venous trauma (e.g., perforation, dissection, erosion)
- Prolonged exposure to fluoroscopic radiation
- Renal failure from contrast media used to visualize coronary veins

7 ALTERNATE PRACTICES AND PROCEDURES

Patients who require an ICD and also have heart failure are routinely treated with a commercially available ICD and medications. Medications include both those to treat arrhythmias and medications to treat heart failure. Additional medical treatments for heart failure include, but are not limited to, exercise and nutrition programs. Alternative therapies for the treatment of ventricular arrhythmias, as deemed appropriate by the physician based upon electrophysiological (EP) testing and other diagnostic evaluation, include antiarrhythmic medication, electrical ablation, cardiac surgery, and electronic devices including pacemaker and other commercially available ICD systems, or a combination thereof.

8 MARKETING HISTORY

The CONTAK CD CRT-D System and the EASYTRAK lead (Models 4510/4511/ 4512/4513) are distributed commercially outside the United States. These devices are approved for sale in the European Economic Community, Australia, New Zealand, Canada, Hong Kong, Singapore, Indonesia, Lebanon, Malaysia, Malta, Mexico, Israel, Egypt, Saudi Arabia, Turkey, Czech Republic, Slovakia, Slovenia, India, South Africa, and Latin America (Argentina, Bolivia, Chile, Columbia, Dominican Republic, Ecuador, Panama, Venezuela, Uruguay).

Neither the CONTAK CD CRT-D System nor the EASYTRAK leads have been withdrawn from market in any country for any reason related to the safety and effectiveness.

9 SUMMARY OF PRE-CLINICAL STUDIES

Prior to initiation of clinical studies, Guidant conducted the following bench testing (i.e., components, assemblies, device system and software tests), biocompatibility evaluation,

sterilization validation, and animal studies on the CONTAK CD CRT-D System. These studies were performed in accordance with established national and international industry standards such as ANSI/AAMI PC69:2000; ISO 5841-3: 1992(E); ISO 11318:1993(E); prEN45502 Active Implantable Medical Devices, Part 2-1 (Requirements for active implantable medical devices intended to treat bradyarrythmia), (draft) November 1996; and the Association for the Advancement of Medical Instrumentation (AAMI) Pacemaker Standard, August 1975; or Guidant's product specification. The test results demonstrated that the CONTAK CD CRT-D pulse generator, EASYTRAK lead and the entire CONTAK CD CRT-D system met the requirements set by these standards (sections that apply, as outlined in the following tables), and Guidant's specifications. The following tables provide brief descriptions of the verification and validation tests conducted on the CONTAK CD CRT-D system and EASYTRAK® lead.

9.1 PULSE GENERATOR: DESIGN VERIFICATION TESTING (DVT)

The design verification testing of the CONTAK CD CRT-D Model 1823 pulse generator included component, electronic and mechanical tests (including packaging and shipping), electromagnetic compatibility evaluation, battery capacity test, pulse generator software design verification and programmer software application tests as described below:

Component Testing: Except for the lead connector assembly, the major components for the CONTAK CD CRT-D pulse generator are identical to the legally marketed VENTAK AV III DR (PMA P960040). The lead connector assembly was modified to include three new components, the header, the outer lead seals, and the IS-1/LV-1 Connector Block. These new components were tested and passed (Table 3).

Table 3: Component Testing

Summary of Component Testing*	Sample Size	Test Results (Pass/Fail)
Header: Visual inspection, dimensional analysis, thermal shock, high temp/high humidity storage, cytotoxicity, pyrogenicity, material analysis.	1 to 35	Pass
Outer Lead Seals: Visual inspection, dimensional inspection; cytotoxicity, pyrogenicity, material analysis.	1 to 105	Pass
IS-1/LV-1 Connector Block: Visual inspection, dimensional inspection, material analysis.	1 to 32	Pass
*Materials used in these components were tested and met the requirements of ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing (1997)		

Electronic and Mechanical Design Verification Tests: Because of the similarity (same electronics and firmware) between the legally marketed VENTAK AV III DR and the CONTAK CD CRT-D pulse generator, electrical design verification testing for the VENTAK AV III DR applies to the CONTAK CD CRT-D pulse generator and was not repeated. Mechanical design verification test was performed on CONTAK CD CRT-D devices that were exposed to a representative manufacturing process, including sterilization cycles and vibration tests (Table 4).

Table 4: Pulse Generator Design Verification Testing

Summary of Pulse Generator DVT	Sample Size	Test Results (Pass/Fail)
Electronic Design Verification Testing		
Tests were conducted on the VENTAK AV III DR at three different stages of the pulse generator: welded PG assembly, PG assembly with external battery connections, and hybrid system board. Tests were conducted in the following functional areas: Telemetry operation, sensing, pacing, shocking, magnet, beeper, electrograms, device clock, battery status, and faults/error handling.	5	Pass
Mechanical Design Verification Testing		
Tests were conducted on the CONTAK CD CRT-D in the main functional areas: mechanical requirements, environmental tests, and package and shipping tests. Such tests included internal atmosphere and hermeticity, connector assembly lead and adapter compatibility, thermal shock and cycling, vibration, and dimensional analysis. The IS-1/DF-1/LV-1 connector assembly met requirements of ISO 5841-3: 1992(E) and ISO 11318: 1993(E).	1 to 10	Pass
Packaging and Shipping tests were done to ensure that the device remains damage free and that the package remains functional while in transit and storage mode prior to implant. Labeling must remain legible.	4	Pass

Electromagnetic Compatibility (EMC) Evaluation: The CONTAK CD CRT-D Model 1823 pulse generator was evaluated to ensure that the device will operate safely in the presence of commonly encountered electromagnetic interference (EMI) such as cellular phones, cordless phones, electronic article surveillance systems (EASS), and radios designed for the home (provided labeled guidances are adhered to). Testing was based on prEN45502 Active Implantable Medical Devices, Part 2-1: Requirements for active implantable medical devices intended to treat bradyarrythmia (cardiac pacemakers) Version 9.0, draft Nov. 1996 and the AAMI Pacemaker Standard, August 1975. Since the CONTAK CD CRT-D pulse generator uses the same electronics and device firmware as the legally marketed VENTAK AV III DR, test results from the VENTAK AV III DR apply to the CONTAK CD CRT-D. A subset of tests was repeated on the CONTAK CD CRT-D to evaluate the effects of adding the left ventricular lead (Table 5).

Table 5: Electromagnetic Compatibility (EMC) Testing

Summary of Electromagnetic Compatibility (EMC) Testing	Sample Size	Test Results (Pass/Fail)
VENTAK AV III DR pulse generator performance was evaluated when subjected to the following:	3	Pass*
• Radiated radio frequency; pulsed and continuous wave up to 200 V/m field strength, (27, 72, 450, 900, 1800, 2450, and 3100 MHz) based on the AAMI pacemaker standard, Aug 1975. • Testing at 27 & 72 MHz was repeated for the CONTAK CD CRT-D.*		
• Conducted frequency from 16.6 Hz to 50 MHz as defined in prEN45502 Active Implantable Medical Devices. Part 2-1Requirements for active implantable medical devices intended to treat bradyarrythmia (cardiac pacemakers). Version 9.0.		
• High voltage external defibrillation shocks.		
• Exposure to electrostatic discharge pulses.		
• Exposure to Electronic Article Surveillance Systems (EASS) per Georgia Technical Institute EASS test protocol for Implantable Medical Devices, Version 2.0.		
• Exposure to electrocautery		
• Exposure to static magnetic fields up to 10mT (the reed switch is activated/ deactivated when the field is maintained at >1.0mT.)		
Summary of Cellular Telephone Testing for VENTAK AV III DR		
Resistance to Interference from Cellular Telephones (450 MHZ to 1100 MHz)	1	Pass
Resistance to Interference from Cellular Telephones (850 MHZ to 2500 MHz)	1	Pass
Resistance to Interference from Cellular Telephones U. S. Cellular telephones. (NADC = TDMA-50) (MIRS = TDMA-11)	1	Pass
The CONTAK CD CRT-D was also tested for EMI simulating cellular phone emissions per the ANSI/AAMI PC69:2000 (Active Implantable Medical Devices - Electromagnetic Compatibility (EMC) test protocols for Implantable Cardiac Pacemakers and Implantable Cardioverter Defibrillators.)	3	Pass

*Guidant reported that there were no instances of memory errors, parameter changes, reset conditions or damage from any test. Three devices showed the expected reversion to noise mode in the presence of conducted signals of sufficient amplitude and frequency. Three devices showed susceptibility to pulsed RF at 27 MHz and slight susceptibility to pulsed RF at 72 MHZ; these levels are comparable to other legally marketed implantable defibrillator devices.

Battery Capacity Test: The CONTAK CD CRT-D battery is identical to the VENTAK AV III DR battery; therefore, the VENTAK AV III DR battery testing applies to the CONTAK CD CRT-D and was not repeated. However, a Battery Capacity Test was performed for the CONTAK CD CRT-D pulse generator to establish the usable capacity of the cell (battery) and the reserve capacity between ERI (Elective Replacement Indicator) and EOL (End Of Life) when used with the pulse generator's electronics (Table 6).

Table 6: Battery CapacityTesting

Summary of Battery CapacityTesting	Sample Size	Test Results (Pass/Fail)
The Battery Capacity Test used a set of calculations, with data provided by the battery manufacturer and data measured in Guidant's laboratory, to calculate usable battery capacity. The battery met Guidant specification.	6 flex assemblies and 6 sets of batteries	Pass

Pulse Generator Software Design Verification Test: The CONTAK CD CRT-D pulse generator software (also known as firmware) is identical to the VENTAK AV III DR pulse generator software. Design verification testing of the software incorporated in the CONTAK CD CRT-D pulse generators encompassed two different areas: the Flash EPROM and the Read-Only Memory on the chip (microcontrol) (Table 7).

Table 7: Pulse Generator Software Design Verification Test

Summary of Pulse Generator Software Design Verification Test: (from VENTAK AV III DR)	Sample Size	Test Results (Pass/Fail)
Using an automated test system, the testing verified the proper operation and interaction of the various tasks to be executed by the software (according to the test requirements specification) to ensure proper function, timing, and data exchange. The firmware version number is 1.0.02.	PG Software	Pass

Model 2848 Software Application Design Verification Test: Design verification testing of the Model 2848 Programmer Software Application (the PRM Software, Version 3.1) was performed to ensure that the software meets the functional software requirements specifications. Testing was conducted with either a CONTAK CD CRT-D system including a CONTAK CD CRT-D Model 1823 pulse generator and a Model 2920 PRM (Programmer, Recorder, Monitor) with the Model 2909 Multiple Application Utility (MAU) and Model 2848 Software Application installed on it, or the same system with a pulse generator simulator replacing the CONTAK CD CRT-D pulse generator (Table 8).

Table 8: Model 2848 Software (Version 3.1) Application DVT

Summary of Model 2848 Software Application DVT	Sample Size	Test Results (Pass/Fail)
Testing includes the functional software requirements associated with each window/feature. The software version number is Version 3.1 for use with the Model 2920 PRM.	PG Software	Pass with 2 anomalies*

*1) Under certain circumstances at the end of a pacing threshold test, after pulling the telemetry wand out of range, a text box indicating "Out of Range/Telemetry Noise" remains and threshold values will not display on the dialog window until the wand is replaced; this is not expected to occur under actual use. 2) Under certain circumstances when

the PRM is in disk mode, the Last Interrogation Date field is blank on the Battery Status screen and in the printed report. These anomalies have no effect on therapy or patient safety.

9.2 EASYTRAK LEAD: DESIGN VERIFICATION TESTING

Electrical and mechanical integrity of the EASYTRAK lead were performed to demonstrate conformance to a battery of lead tests and are summarized below (Table 9). All leads were preconditioned with shelf life, temperature cycling, and shipping test conditions prior to functional testing.

Table 9: EASYTRAK Lead DVT

Summary of EASYTRAK Lead DVT	Sample Size	Test Results (Pass/Fail)
Full Lead Testing:		
Packaging visual verified that the packaging met the requirements of the sterile pack and final pack engineering documents.	12	Pass
Guide Catheter Compatibility testing verified that the EASYTRAK Lead passed through the EASYTRAK guide catheters with no damage to the lead or guide catheter.	48	Pass
Guide Wire Compatibility testing verified that all 0.014" guide wires indicated for use with the EASYTRAK Lead passed through the lead and guide catheter and could be withdrawn from the lead with no damage to the lead or guide wire.	48	Pass
Finishing Wire Compatibility testing verified that the finishing wire could track to the transition of the lead and was able to be withdrawn from the lead with no damage to the lead or finishing wire.	48	Pass
Axial Load testing verified that the lead can withstand implant forces and demonstrated compliance to the requirements defined by prEN 45502-2-1, section 23.3. (draft Nov. 96).	48	Pass
Electrical Resistance: DC Resistance was required to be between 10 and 22 ohms.	12	Pass
Insulation Integrity Pressure testing verified the integrity of the insulation. Leads were pressurized to 14 ± 2 PSI with dry nitrogen; leads must not exhibit evidence of nitrogen leakage.	12	Pass
Pacing Impedance: was tested per the prEN 45502-Part 2-1, (draft Nov. 96).	12	Pass
LV-1 Terminal Testing: The LV-1 connector is a proprietary connector designed for compatibility with Guidant pulse generators with an LV-1 port.		
LV-1 Insertion/Withdrawal: this test verified that the LV-1 terminal meets maximum insertion/withdrawal requirements per ISO 11318:1993(E).	12	Pass
LV-1 Pin Setscrew Deformation: this test verified that set screw forces can not deform the lead connector to the extent that insertion and withdrawal forces become excessive.	12	Pass
LV-1 Low Voltage Seal Integrity: this test verified that the LV-1 connector seal rings could electrically isolate the pin and the external environment.	12	Pass
LV-1 High Voltage Seal Integrity: this test verified that the LV-1 connector seal rings could electrically isolate the pin and the external environment under high voltage conditions.	12	Pass

Summary of EASYTRAK Lead DVT	Sample Size	Test Results (Pass/Fail)
Flex Fatigue Testing:		
LV-1 Connector Flex Fatigue testing assessed the fatigue resistance of the LV-1 terminals and demonstrated conformance to the prEN 45502 Part 2-1 Connector Flex Test, Section 23.5 Test 2 (draft Nov. 1996).	12	Pass
Bell Mouth Flex Fatigue Test of Lead Conductor verified compliance of the lead conductor with the requirements of prEN 45502 Section 23.5 Test 1 (draft Nov. 1996).	12	Pass
Buckle Flex Fatigue Test of Lead Body Conductor verified the ability of the lead body conductor to withstand ten years (420 million cycles) of flexing.	12	Pass
Manufacturing Process Validation for Bond/Weld/Strength Testing:		
All welded electro-mechanical connections must withstand a minimum assembly joint pull force. All load-bearing molded and bonded connections must have a minimum dry pull strength. The dry retention force between the steroid collar and electrode molding must also meet the minimum force per specifications.	12	Pass

9.3 SYSTEM: DESIGN VALIDATION TESTING

Design validation testing that was conducted on the CONTAK CD CRT-D system included system features tests and a simulated use test (field study). In addition, an animal study carried out under Good Laboratory Practices was also conducted pre-clinically (Table 10).

Table 10: System Design Validation Testing

System Design Validation Testing	Sample Size	Test Results (Pass/Fail)
System Features Tests: Tests were conducted to exercise major features of the CONTAK CD CRT-D system. Each test demonstrated the functionality of a given feature and verified that the programmer had properly loaded parameters into the pulse generator. Feature groups tested included device family, programmer support, lead support, tachy modes, tachyarrhythmia detection, tachyarrhythmia therapy, bradycardia modes, bradycardia therapy, diagnostics, and faults/error handling. The system performed as expected based on the specifications.	2 systems consisting of CONTAK CD CRT-D PG and programmer software.	Pass
Simulated Use Test: From a field user perspective, Guidant field clinical engineers evaluated the performance of the CONTAK CD CRT-D system and EASYTRAK lead and verified that the labeling/manuals were easily understood and the entire CONTAK CD CRT-D system and EASYTRAK lead performed as expected during clinical use. Clinical scenarios were simulated using the pulse generator, programmer (PRM), PRM software, a cardiac signal simulater, and the EASYTRAK lead and accessories (guide catheter, guidewire, and finishing wire).	2 users performed tests.	Pass
Animal Study: Study verified that the CONTAK CD CRT-D system and EASYTRAK leads including CONTAK CD CRT-D Model 1823 pulse generator, EASYTRAK lead, guide catheter, occluding guiding catheter, guidewire, finishing wire, lead stabilizer, LV-1 Port Plug, LV-1 Adapter, and Model 2848 software, along with a commercially available atrial pace/sense lead and a ventricular pace/sense/shocking lead, were compatible and performed safely in an *in-vivo* canine model. Testing demonstrated that the system performed safely in an *in-vivo* animal model.	3 animals	Pass

9.4 CONTAK CD CRT-D SYSTEM & EASYTRAK LEAD: SAFETY AND RISK ANALYSIS

The safety and risk analysis of the CONTAK CD CRT-D system was conducted to identify potential hazards and their causes, and to take appropriate actions to minimize patient and user risk. Analysis included the following:

Hazard Analysis: Hazard Analysis identified potential hazards with using the system devices and documented the response taken to control the probability of occurence or to minimize the risk. Potential hazards were peer reviewed for adequacy of the mitigation; residual risk was deemed acceptable.

Failure Modes and Effects Criticality Analysis (FMECA): FMECA identified potential design, test, or process inadequacies that could adversly affect the safety and performance of the device and recommended corrective actions to eliminate or minimize

these inadequacies. Three recommendations were identified and were incorporated into device testing scheme.

Reliability Prediction Analysis: The Reliability Prediction Analysis was performed using field performance failure rates of similar pulse generators along with the "Parts Stress Analysis Prediction" procedure in MIL-HDBK-217F in the absence of field performance data. The analysis resulted in an expected field performance of 0.1461% failures/month.

9.5 BIOCOMPATIBILITY EVALUATION

The biocompatibility of the tissue contacting materials used in the CONTAK CD CRT-D pulse generator, and the EASYTRAK lead and lead accessories was established in previous PMA applications (P890061, P910077, P960040 and P910073, P950001, P960060 respectively). Pulse generator materials include: polyurethane, titanium, and silicone rubber that are all currently used in Guidant's commercially available ICD devices.

Materials used in the EASYTRAK lead that have direct long-term tissue or blood contact include: titanium, platinum, silicone rubber (including silicone rubber with titanium oxide pigment), polyurethane, and polytetrafluroethylene (PTFE). In addition, the drug collar contains Dexamethasone Acetate in liquid silicone rubber. The biocompatibility of titanium, platinum, silicone rubber, and Dexamethasone Acetate has been established in previous PMA applications (P910073, P950001, P960060). Materials that have a new use in the EASYTRAK lead include silicone rubber with titanium oxide pigment, polyurethane, and PTFE. Guidant performed biocompatibility testing on these materials and all were determined to be biocompatible. Biocompatibility testing included cytotoxicity, hemolysis, Ames Mutagenicity, and acute and chronic system toxicity.

Materials used in the CONTAK CD CRT-D pulse generator, and the EASYTRAK lead and lead accessories were tested and met the requirements of ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing (1997).

9.6 STERILIZATION VALIDATION

Sterilization assessments were performed and validated that the CONTAK CD CRT-D Model 1823 pulse generator, EASYTRAK leads, and system accessories can be effectively sterilized with the Getinge Oxyfume 2000® or the 100% ethylene oxide (EtO) sterilization process. These processes are identical to those used for Guidant's commercially available ICD pulse generators and leads.

For the CONTAK CD CRT-D Model 1823 pulse generator, the sterility assurance factor (SAL) was estimated to be 10^{-24}. For the EASYTRAK lead, suture sleeve, LV-1 Lead Cap, LV-1 Lead Port Plug, and Model 6744 Lead Adapter the SAL was estimated to be 10^{-16}. For the Finishing Wire, the SAL was estimated to be 10^{-37}.

9.7 ANIMAL STUDIES

Guidant conducted an animal study in compliance with Good Laboratory Practice (GLP) regulations (21 CFR, Part 58) with the CONTAK CD CRT-D system in an *in-vivo* canine model to demonstrate that the system meets user needs and intended uses. The animal study also addressed the compatibility of the system components and verified that the components of the CONTAK CD CRT-D system were compatible, and the system performed safely for its intended use.

In addition to the system study described above, Guidant conducted a series of animal studies to verify that the EASYTRAK lead is safe for chronic implantation. These studies demonstrated that the EASYTRAK lead is biocompatible and biostable after chronic (six months) implantation in canines and that the lead remains in position once implanted.

9.8 SHELF LIFE FOR PMA DEVICES

Table 11: Device Shelf Life

Device	Shelf Life
CONTAK CD CRT-D pulse generator, Model 1823	Expiration dating for this device has been established and approved at 1 year from the battery-attach date.
EASYTRAK Lead, 4510, 4511, 4512, 4513	Expiration dating for this device has been established and approved at 2 years from the date of sterilization.
Accessory: • Finishing Wire, Models 6730, 6731, 6732, 6733	Expiration dating for this device has been established and approved at 2 years from the date of sterilization.
Accessories: • Suture Sleeve, Model 6741 • LV-1 Lead Cap, Model 6742 • LV-1 Lead Port Plug, Model 6742 • Lead Adapter, Model 6744	Expiration dating for these devices has been established and approved at 4 years from the date of sterilization.

10 SUMMARY OF CLINICAL STUDIES

Guidant conducted the CONTAK CD Study to demonstrate the safety and effectiveness of the CONTAK CD CRT-D system and to demonstrate a reasonable assurance of the safety and effectiveness of biventricular stimulation, or cardiac resynchronization therapy (CRT), using the Guidant Model 1822 VENTAK CHF AICD and Model 1823 CONTAK CD CRT-D pulse generator along with the EASYTRAK (Models 4510/4511/4512/4513) coronary venous steroid-eluting single-electrode pace/sense lead.

The CONTAK CD Study failed to prospectively demonstrate effectiveness of the CRT function of the device. The CONTAK CD Study met the Lead and System Effectiveness endpoints as well as the Lead and System Safety endpoints (as defined on page 22). Subgroup analysis revealed a population of patients that had Class III/IV heart failure at the time of randomization that appeared to have improvements on certain functional endpoints, including the peak VO2 and the six minute hall walk. A second study was performed (Focused Confirmatory Study) using this subgroup of patients to confirm the effectiveness of CRT.

10.1 CONTAK CD STUDY

10.1.1 STUDY DESIGN

The CONTAK CD Study was a prospective randomized, controlled, multicenter, double-blind study conducted at 47 sites in the United States and enrolled a total of 581 patients. All patients enrolled were intended to be implanted with a device capable of delivering both CRT and treating ventricular tachyarrhythmias. Patients were randomized to CRT Off (VVI lower rate 40) or CRT On (VDD). The study began as a crossover design (called "Phase I") and enrolled 248 patients with a primary endpoint of functional status with three months of follow-up. The study was later modified to a parallel design (called "Phase II") and enrolled 333 patients with a longer, six-month follow-up. The data from the first three months of the crossover phase were pooled with data from the six-month parallel phase. The visit schedule and testing requirements remained the same. Additionally, while the study originally used the VENTAK CHF AICD in conjunction with epicardial leads placed via thoracotomy, the CONTAK CD CRT-D and EASYTRAK lead (placed transvenously) were added to the protocol later in the study.

10.1.2 INCLUSION/EXCLUSION CRITERIA

Patients enrolled in the study were required to meet the following inclusion criteria:

- Meet the general indication for ICD implant
- Symptomatic heart failure despite optimal drug therapy (ACE inhibitors with diuretic and/or digoxin, as determined to be indicated and tolerated by the patient's physician-investigator)
- Left ventricular ejection fraction ≤ 35%
- QRS duration ≥ 120 ms
- Age ≥ 18 years
- Normal sinus node function

Patients were excluded from the investigation if they met any of the following criteria:

- Meet the general indications for permanent antibradycardia pacing, including pacemaker dependence
- Have chronic, medically refractory atrial tachyarrhythmias
- Require concomitant cardiac surgery
- Are unable to undergo device implant, including general anesthesia if required

- Are unable to comply with the protocol and follow-up requirements, including exercise testing
- Have a life expectancy of less than six months due to other medical conditions
- Have amyloid disease (amyloidosis)
- Have hypertrophic obstructive cardiomyopathy
- Require in-hospital continuous intravenous inotropes
- Have pre-existing cardioversion/defibrillation leads other than those specified in the investigational plan (unless the investigator intends to replace them with permitted cardioversion/defibrillation leads)
- Women who are pregnant or not using medically accepted birth control
- Have a mechanical tricuspid prosthesis
- Involved in other cardiovascular clinical investigations of active therapy or treatment

10.1.3 FOLLOW-UP SCHEDULE

Pre-implant visit	Initial assessment of patient eligibility; taking of patient history.
Implant	Implant of investigational devices and acute device testing. Randomization status (CRT or No CRT) was assigned for implementation after a 30-day Recovery Period.
Recovery Period	Minimum 30-day period over which the patient recovered from the implant procedure and had his/her heart failure medications adjusted, but with no CRT regardless of the randomization assignment.
Post-Recovery Visit	First visit after the Recovery Period in which patients underwent Special Testing* to establish their baseline condition, after which the randomization assignment was implemented (CRT or No CRT).
Three- and six-month Visits	Evaluation of randomized therapy with Special Testing* and device function at three- and six-months after the Post-Recovery Visit.
Quarterly Visits	After the six-month visit, patients were seen for routine evaluation of device function and patient condition.

* Special Testing included a Symptom-Limited Treadmill Test with measurement of oxygen uptake (Peak VO_2), a Six-Minute Walk, Echocardiography, Holter monitoring, blood chemistry testing, and a Quality of Life (QOL) questionnaire.

10.1.4 PATIENT GROUPS

The CONTAK CD Study included patients with symptomatic heart failure despite optimal drug therapy as defined in the inclusion criteria. This population included patients who were NYHA Class II, III, or IV at the time of implant.

Based upon the clinical results from the covariate analyses in this study, and the internal consistency of these clinical findings with those from other completed CRT studies, the patient subgroup with NYHA Class III/IV heart failure in this study was examined further.

All Patients: All patients (NYHA Class II/III/IV at the time of implant) implanted with an investigational system (N=501). Ten patients died and one withdrew before the Post-Recovery Visit. Therefore, therapy effectiveness analyses used N=490.

NYHA Class III/IV (Advanced Heart Failure): This subgroup was defined as those patients with moderate to severe heart failure at the time of the Post-Recovery Visit (N=227). A percentage of patients either had an improvement or worsening of their NYHA Class during the post-implant recovery period. The patients in the Advanced Heart Failure subgroup were only those who remained in NYHA Class III/IV at the end of the post recovery period. This subgroup was determined from interaction analysis of pre-selected covariates with the functional status endpoints.

10.1.5 ENDPOINTS

The CONTAK CD Study had three investigational elements consisting of:

CRT Effectiveness:

Primary: Composite endpoint consisting of all-cause mortality, hospitalization for heart failure, and ventricular tachyarrhythmia requiring device intervention.

Secondary: Peak VO_2 derived from a symptom-limited exercise test and Quality of Life as measured by the Minnesota Living with Heart Failure Questionnaire©.

Additional: Six-Minute Walk, NYHA Class, Echocardiographic Analysis, Change in Norepinephrine, and Change in Heart Rate.

Lead and System Effectiveness:

Lead: Left ventricular pacing thresholds, biventricular sensing, biventricular lead impedance, and lead placement success rate.

System: VF detection time, biventricular antitachycardia pacing (ATP) efficacy.

Lead and System Safety:

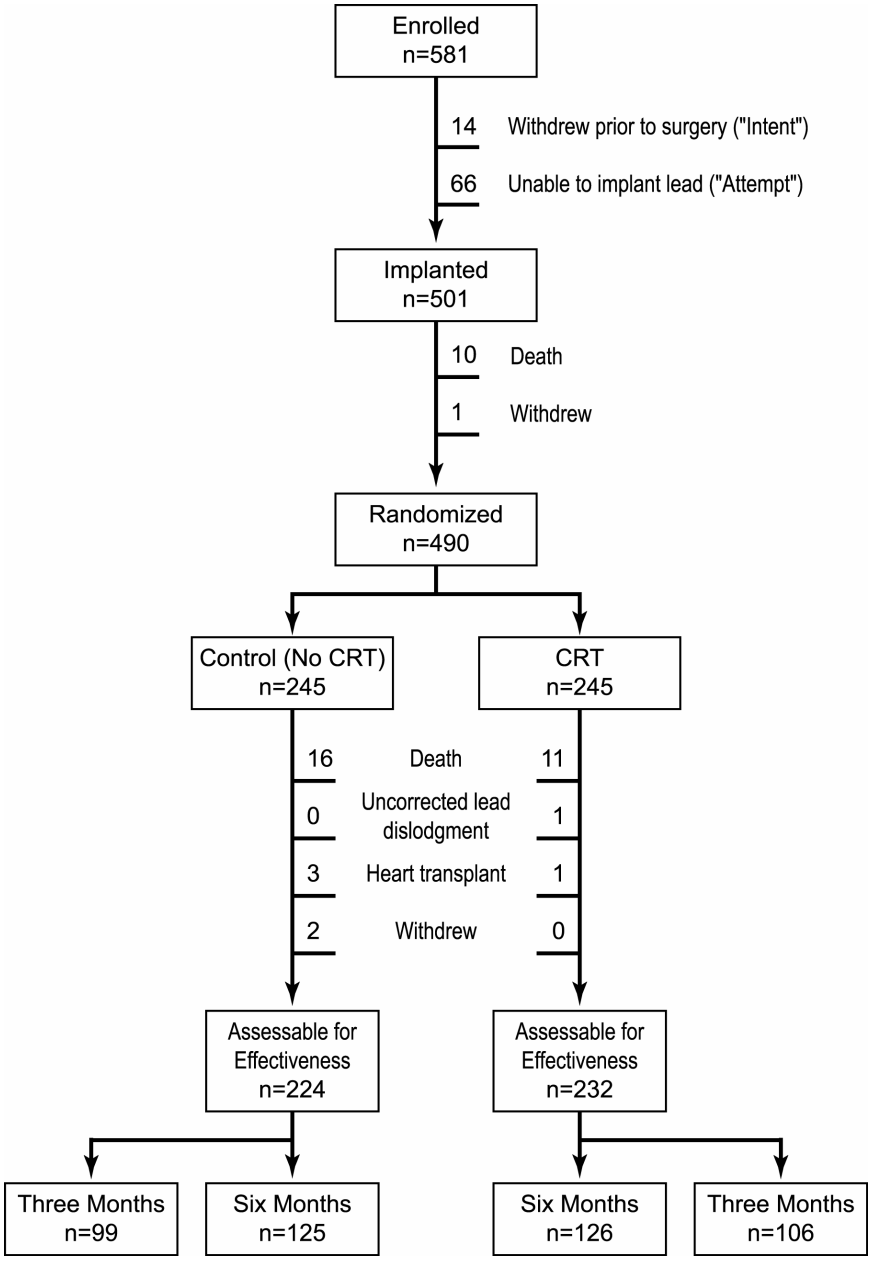
Lead: Incidence of lead-related adverse events.

System: Incidence of severe, device-related adverse events and operative mortality.

10.1.6 STUDY RESULTS

10.1.6.1 PATIENT ACCOUNTABILITY

Figure 1: Enrollment and Follow-Up of Randomized Patients



10.1.6.2 BASELINE CHARACTERISTICS

Table 12: Pre-Implant Assessment

All patients implanted, N=501

Characteristic		All Patients			NYHA Class III/IV		
		CRT (N=248)	No CRT (N=253)	P-val*	CRT (N=117)	No CRT (N=110)	P-val*
Age at Implant (years)	N	248	253		117	110	
	Mean +/- SD	66.0 +/- 10.5	66.3 +/- 10.5	0.73	66.1 +/- 10.5	65.8 +/- 10.5	0.80
	Range	26.1 - 82.6	29.5 - 86.3		26.1 - 82.5	38.3 - 85.3	
Gender [N (%)]	Male	210 (84.7)	211 (83.4)	0.70	90 (76.9)	86 (78.2)	0.82
	Female	38 (15.3)	42 (16.6)		27 (23.1)	24 (21.8)	
NYHA Class [N (%)]	II	80 (32.3)	83 (32.8)	0.66	20 (17.1)	11 (10.0)	0.08
	III	148 (59.7)	144 (56.9)		85 (72.6)	78 (70.9)	
	IV	20 (8.1)	26 (10.3)		12 (10.3)	21 (19.1)	
Concomitant Medications [N (%)]	ACE or ARB	212 (85.5)	224 (88.5)	0.31	95 (81.2)	98 (89.1)	0.10
	Beta Blocker	119 (48.0)	117 (46.2)	0.70	53 (45.3)	44 (40.0)	0.42
	Digoxin	172 (69.4)	171 (67.6)	0.67	84 (71.8)	75 (68.2)	0.55
	Diuretic	217 (87.5)	210 (83.0)	0.16	108 (92.3)	95 (86.4)	0.15
Qualifying LVEF (%)	N	248	253		117	110	
	Mean +/- SD	21.4 +/- 6.6	21.5 +/- 6.7	0.74	20.6 +/- 6.4	21.1 +/- 6.2	0.61
	Range	5.0 - 35.0	10.0 - 35.0		8.0 - 35.0	10.0 - 35.0	
PR Interval** (ms)	N	224	222		107	91	
	Mean +/- SD	205 +/- 42	202 +/- 49	0.44	204 +/- 41	200 +/- 54	0.60
	Range	88 - 336	104 - 400		136 - 336	110 - 400	
Qualifying QRS Duration** (ms)	N	226	224		109	93	
	Mean +/- SD	160 +/- 27	156 +/- 26	0.06	164 +/- 27	152 +/- 24	<0.01
	Range	120 - 240	120 - 264		120 - 240	120 - 222	
Resting Heart Rate (bpm)	N	248	253		117	110	
	Mean +/- SD	73 +/- 12	75 +/- 14	0.37	75 +/- 13	74 +/- 15	0.61
	Range	43 - 108	48 - 120		43 - 108	50 - 120	
Systolic Blood Pressure (mmHg)	N	247	253		116	110	
	Mean +/- SD	118 +/- 21	118 +/- 21	0.95	116 +/- 20	117 +/- 23	0.72
	Range	79 - 197	70 - 190		79 - 191	74 - 190	
Diastolic Blood Pressure (mmHg)	N	247	253		116	110	
	Mean +/- SD	67 +/- 12	69 +/- 12	0.27	68 +/- 12	67 +/- 14	0.85
	Range	31 - 100	40 - 109		31 - 100	40 - 109	

* P-values for comparing means were calculated with Student's t-test; p-values for comparing proportions were calculated with Pearson's chi-squared test.

** PR interval and QRS duration were not obtained for thoracotomy patients

Table 13: Pre-Implant History

All patients implanted, N=501

Characteristic		All Patients			NYHA Class III/IV		
		CRT (N=248)	No CRT (N=253)	P-val*	CRT (N=117)	No CRT (N=110)	P-val*
Primary Tachy Arrhythmia [N (%)]	Monomorphic VT (MVT)	148 (59.7)	136 (53.8)	0.44	72 (61.5)	48 (43.6)	0.03
	Polymorphic VT (PVT)	16 (6.5)	20 (7.9)		7 (6.0)	7 (6.4)	
	Nonsustained VT	58 (23.4)	63 (24.9)		30 (25.6)	35 (31.8)	
	Ventricular Fibrillation (VF)	26 (10.5)	32 (12.6)		8 (6.8)	18 (16.4)	
	Other	0 (0.0)	2 (0.8)		0 (0.0)	2 (1.8)	
Other Arrhythmias [N (%)]	Paroxysmal Atrial Fib.	43 (17.3)	62 (24.5)	0.05	21 (17.9)	29 (26.4)	0.13
	Atrial Flutter	10 (4.0)	13 (5.1)	0.55	3 (2.6)	7 (6.4)	0.16
Arrhythmia/ Conduction Disorder [N (%)]	LBBB	133 (53.6)	138 (54.5)	0.83	59 (50.4)	59 (53.6)	0.55
	RBBB	35 (14.1)	31 (12.3)		21 (17.9)	14 (12.7)	
	Non-Specific	80 (32.3)	84 (33.2)		37 (31.6)	37 (33.6)	
Etiology [N (%)]	Ischemic	167 (67.3)	178 (70.4)	0.47	76 (65.0)	78 (70.9)	0.34
	Non-Ischemic	81 (32.7)	75 (29.6)		41 (35.0)	32 (29.1)	

* P-values were calculated with Pearson's chi-squared test

10.1.6.3 CRT EFFECTIVENESS

10.1.6.3.1 Heart Failure Progression (Composite Index)

The Composite Index (primary endpoint) was a combination of three events: all-cause mortality, hospitalization for heart failure, and VT/VF event requiring therapy. A committee consisting of three heart failure specialists and an electrophysiologist reviewed and adjudicated all patient deaths and all hospitalizations, defined as an admission greater than 23 hours. Outpatient care, emergency room care, and clinic visits less than 23 hours were collected but not considered to be hospitalizations for the purposes of analysis.

Table 14: Composite Index

All patients implanted and active 31 days post-implant

Group	Heart Failure Mortality or Morbidity Event	CRT		No CRT		Relative Reduction with CRT
		N	%	N	%	
All Patients (NYHA II/III/IV) (n=490)	Death from any cause	11	4.5	16	6.5	15% p=0.35
	HF hospitalization	32	13.1	39	15.9	
	VT/VF	36	14.7	39	15.9	
NYHA Class III/IV (n=227)	Death from any cause	11	9.4	11	10.0	22% p=0.23
	HF hospitalization	23	19.7	27	24.5	
	VT/VF	21	17.9	22	20.0	

Twenty-seven patients died during the therapy phase. Mortality stratified by treatment group and cause, as adjudicated by the Events Committee, is shown in Table 15. The Kaplan-Meier (Figure 2) shows total survival by treatment group.

Table 15: Mortality Stratified by Treatment Group and Cause

All patients implanted and active at 31 days post-implant, N=490

Deaths	CRT (N=245)	No CRT (N=245)
Cardiac, pump failure	4 (1.6%)	9 (3.7%)
Cardiac, arrhythmic	1 (0.4%)	0 (0.0%)
Cardiac, other	2 (0.8%)	1 (0.4%)
Non-cardiac	2 (0.8%)	3 (1.2%)
Unknown	2 (0.8%)	3 (1.2%)
Total	11 (4.5%)	16 (6.5%)

Figure 2: Kaplan Meier Curve

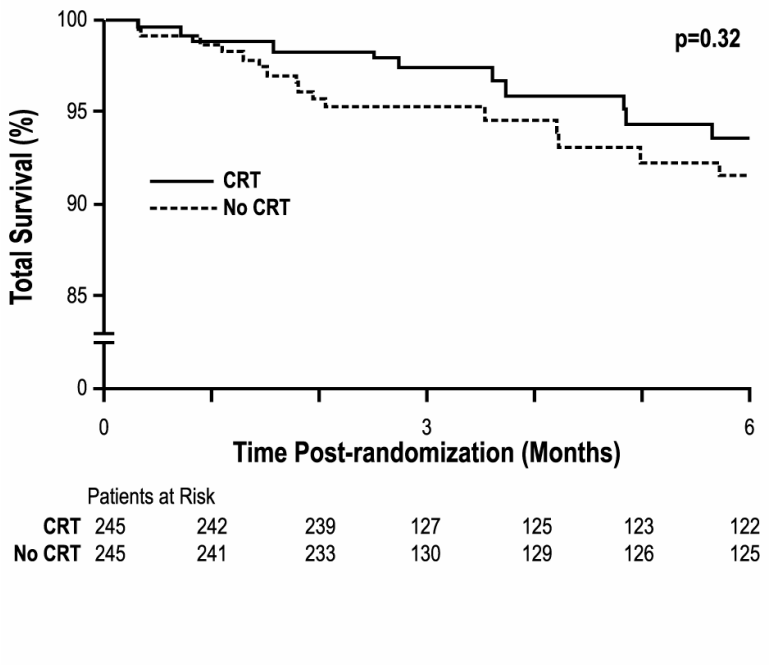


Table 16 presents the reasons for hospitalization within the treatment period as determined by the Events Committee.

Table 16: Patients Hospitalized during Treatment Period*

All patients implanted and active at 31 days post-implant, N=490

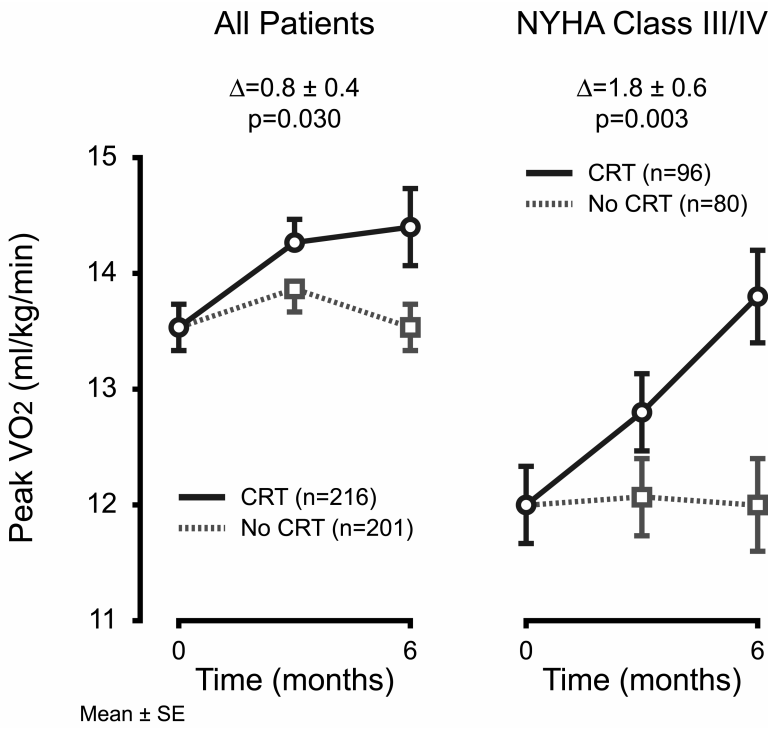
Reason for Hospitalization	All Patients			NYHA Class III/IV		
	CRT (N=245)	No CRT (N=245)	Total (N=490)	CRT (N=117)	No CRT (N=110)	Total (N=227)
Heart Failure	32	39	71	23	27	50
Cardiac - other	20	25	45	14	14	28
Noncardiac	26	19	45	14	14	28
Total Hospitalizations	**66**	**70**	**136**	**40**	**46**	**86**

* Represents number of patients with each category of hospitalization. Patients may have multiple hospitalizations that fall into different categories

10.1.6.3.2 Peak VO2

Peak VO_2 was determined from a standardized protocol for exercise testing as a means of measuring a patient's capacity for performing physical activity.

Figure 3: Change in Peak VO_2



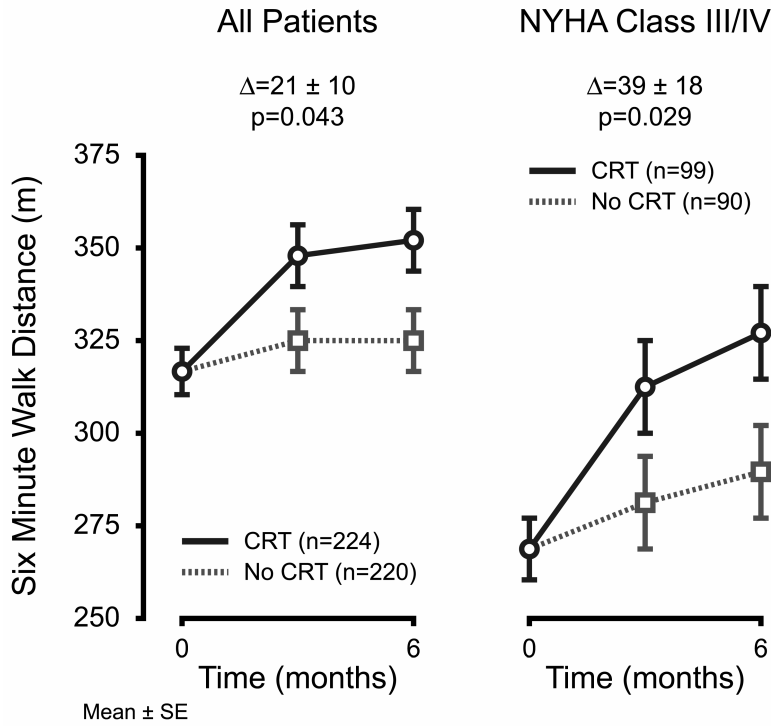
	All Patients			NYHA Class III/IV		
Peak VO_2 (ml/kg/min)	CRT (N=216)	No CRT (N=201)	P-val	CRT (N= 96)	No CRT (N= 80)	P-val*
Post-recovery Visit	13.5 +/- 0.2	13.5 +/- 0.2	-	12.0 +/- 0.3	12.0 +/- 0.3	-
3 Months	14.3 +/- 0.2	13.9 +/- 0.2	0.206	12.8 +/- 0.4	12.1 +/- 0.4	0.084
6 Months	14.4 +/- 0.3	13.6 +/- 0.3	0.030	13.8 +/- 0.5	12.0 +/- 0.5	0.003

**P-values reflect the between-group differences with respect to baseline.*

10.1.6.3.3 Six-Minute Walk

The Six-Minute Walk test is a measure of a patient's ability to sustain exercise during an activity similar to that which a patient may typically perform on a daily basis. For this test, patients are instructed to walk as far as possible in 6 minutes in a level corridor. **Figure 4** provides the change in Six-Minute Walk.

Figure 4: Change in Six Minute Walk



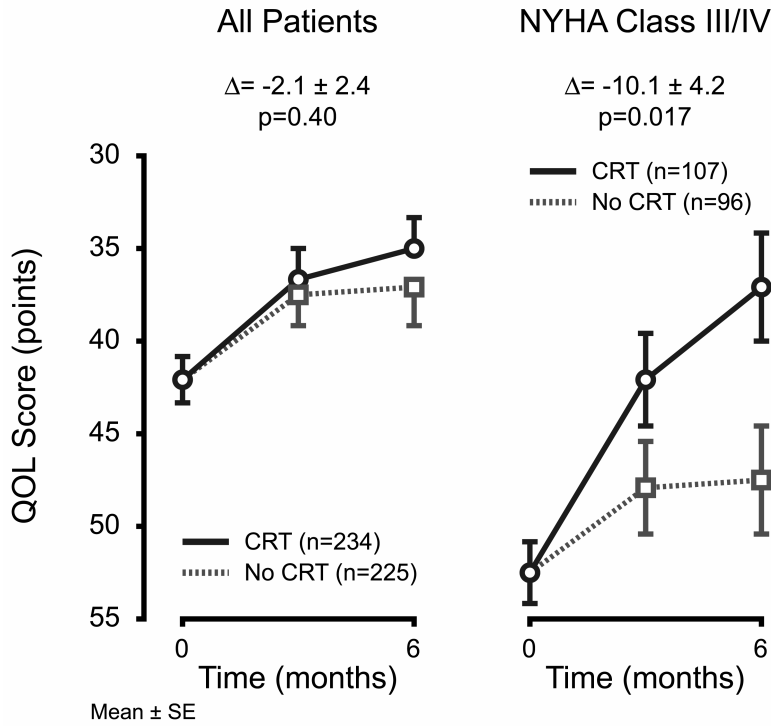
	All Patients			NYHA Class III/IV		
Six Minute Walk Distance (meters)	**CRT (N=224)**	**No CRT (N=220)**	**P-val***	**CRT (N= 99)**	**No CRT (N= 90)**	**P-val***
Post-recovery Visit	317 +/- 5	317 +/- 5	-	268 +/- 9	268 +/- 9	-
3 Months	348 +/- 7	331 +/- 8	0.058	312 +/- 12	280 +/- 12	0.028
6 Months	353 +/- 8	332 +/- 8	0.043	327 +/- 14	288 +/- 15	0.029

**P-values reflect the between-group differences with respect to baseline.*

10.1.6.3.4 Quality of Life

Quality of Life (QOL) (Figure 5) was assessed using the 21 question Minnesota Living with Heart Failure questionnaire. Each question is answered by the patient, ranking each item on a scale ranging from 0 to 5. A lower total score indicates an improved quality of life.

Figure 5: Change in Quality of Life



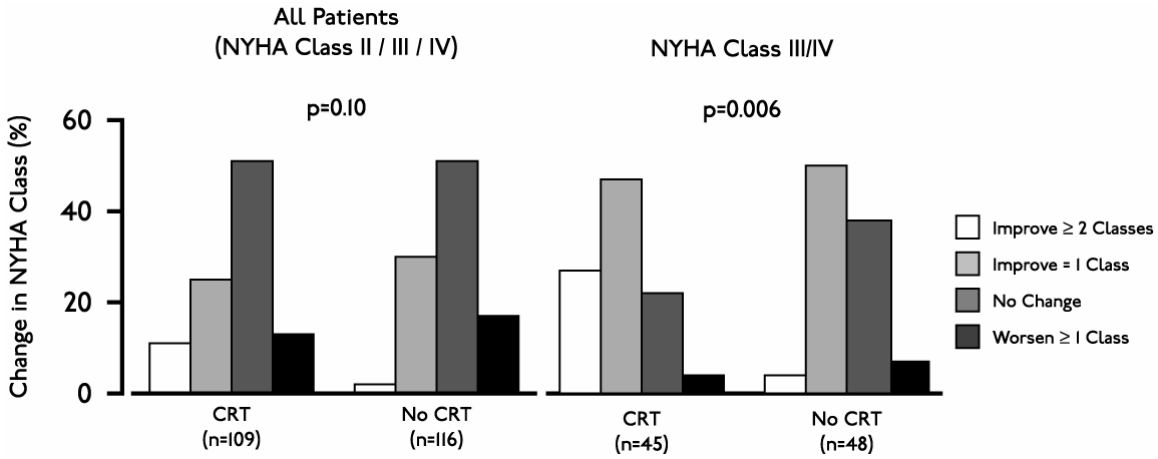
	All Patients			NYHA Class III/IV		
QOL (points)	**CRT (N=234)**	**No CRT (N=225)**	**P-val***	**CRT (N=107)**	**No CRT (N= 96)**	**P-val***
Post-recovery Visit	41.8 +/- 1.1	41.8 +/- 1.1	-	52.7 +/- 1.5	52.7 +/- 1.5	-
3 Months	36.6 +/- 1.5	37.3 +/- 1.6	0.711	41.9 +/- 2.4	47.5 +/- 2.6	0.078
6 Months	34.8 +/- 1.8	36.9 +/- 1.8	0.395	37.2 +/- 3.1	47.3 +/- 3.2	0.017

**P-values reflect the between-group differences with respect to baseline.*

10.1.6.3.5 NYHA Class

The determination for New York Heart Association (NYHA) Class is based on mutual assessment by the patient and the patient's physician of the patient's heart failure symptoms both at rest and while performing ordinary physical activity. NYHA Class was determined at each follow-up visit by a physician who was blinded to the patient's randomized therapy.

Figure 6: Changes in NYHA Class



	All Patients					NYHA Class III/IV				
	CRT (N=109)		No CRT (N=116)		P-val*	CRT (N= 45)		No CRT (N= 48)		P-val*
Change in NYHA Class	N	%	N	%		N	%	N	%	
Improve 2 or More Classes	12	11.0	2	1.7	0.10	12	26.7	2	4.2	0.006
Improve 1 Class	27	24.8	35	30.2		21	46.7	24	50.0	
No Change	56	51.4	59	50.9		10	22.2	18	37.5	
Worsen 1 Class	13	11.9	19	16.4		2	4.4	4	8.3	
Worsen 2 or More Classes	1	0.9	1	0.9		0	0.0	0	0.0	

**P-value was calculated from Mantel-Haenszel test and reflects the between-group differences with respect to baseline.*

10.1.6.3.6 Echocardiography

Several echocardiography (echo) variables were identified to assist in measuring the possible hemodynamic impact of CRT as shown in Table 17. The limitation of this data is that patients are measured while at rest, and therefore, the data may not reflect any hemodynamic benefit that may be observed when patients are exercising and performing their daily activities.

Table 17: Echocardiography Results

		CRT		No CRT		Between Groups	
Parameter	**Timepoint**	**N**	**Mean +/- SE**	**N**	**Mean +/- SE**	**Mean +/- SE**	**P-val**
All Patients							
LVIDd (mm)	Post-recovery Visit	228	70.4 +/- 0.5	219	70.4 +/- 0.5	0	-
	Change at 6 Months	228	-3.4 +/- 0.6	219	-0.3 +/- 0.6	-3.1 +/- 0.9	<0.001
LVIDs (mm)	Post-recovery Visit	228	58.3 +/- 0.5	219	58.3 +/- 0.5	0	-
	Change at 6 Months	228	-4.0 +/- 0.7	219	-0.7 +/- 0.7	-3.3 +/- 0.9	<0.001
LVEF (%)	Post-recovery Visit	222	27.8 +/- 0.3	216	27.8 +/- 0.3	0	-
	Change at 6 Month	222	5.1 +/- 0.7	216	2.8 +/- 0.7	2.4 +/- 1.0	0.020
NYHA Class III/IV							
LVIDd (mm)	Post-recovery Visit	104	71.2 +/- 0.7	92	71.2 +/- 0.7	0	-
	Change at 6 Months	104	-4.9 +/- 1.0	92	-0.2 +/- 1.1	-4.7 +/- 1.5	0.001
LVIDs (mm)	Post-recovery Visit	104	59.2 +/- 0.7	92	59.2 +/- 0.7	0	-
	Change at 6 Months	104	-5.4 +/- 1.1	92	-0.6 +/- 1.1	-4.8 +/- 1.5	0.002
LVEF (%)	Post-recovery Visit	99	26.9 +/- 0.5	91	26.9 +/- 0.5	0	-
	Change at 6 Months	99	6.0 +/- 1.1	91	2.3 +/- 1.2	3.7 +/- 1.7	0.029

10.1.6.3.7 Measures of Sympathetic Tone

Mean Norepinephrine levels (Table 18) and Mean Heart Rate (Table 19) were examined as markers of how CRT may influence the excessive sympathetic drive associated with chronic heart failure.

Table 18: Mean Norepinephrine Results

	All Patients			NYHA Class III/IV		
Norepinephrine (pg/mL)	**CRT (N=228)**	**No CRT (N=217)**	**P-val**	**CRT (N=104)**	**No CRT (N= 90)**	**P-val**
Post-recovery Visit	663 +/- 19	663 +/- 19	-	720 +/- 31	720 +/- 31	-
3 Months	651 +/- 31	681 +/- 32	0.479	685 +/- 55	743 +/- 60	0.463
6 Months	658 +/- 40	738 +/- 41	0.143	681 +/- 75	827 +/- 79	0.163

Table 19: Mean Heart Rate Results

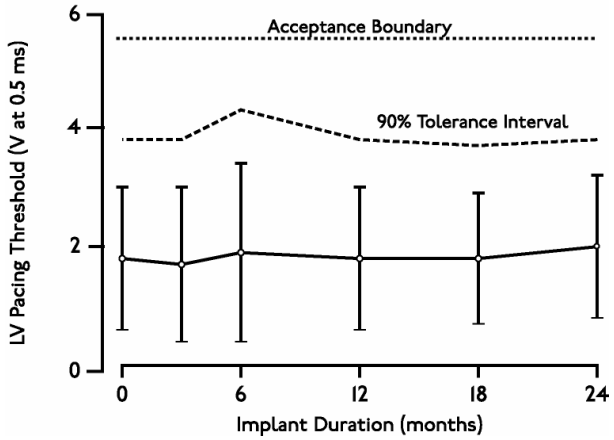
	All Patients			NYHA Class III/IV		
Heart Rate (bpm)	**CRT (N=240)**	**No CRT (N=233)**	**P-val**	**CRT (N=113)**	**No CRT (N=101)**	**P-val**
Post-recovery Visit	72.3 +/- 0.6	72.3 +/- 0.6	-	74.5 +/- 1.0	74.5 +/- 1.0	-
3 Months	70.8 +/- 0.8	72.1 +/- 0.8	0.20	74.1 +/- 1.2	73.9 +/- 1.3	0.94
6 Months	69.4 +/- 1.0	70.2 +/- 1.0	0.58	70.6 +/- 1.6	72.5 +/- 1.6	0.40

10.1.6.4 EASYTRAK LEAD AND SYSTEM EFFECTIVENESS

10.1.6.4.1 Lead Measurements

Figure 7: EASYTRAK Lead Threshold Measurements

All patients implanted with an EASYTRAK lead at first implant, N=443



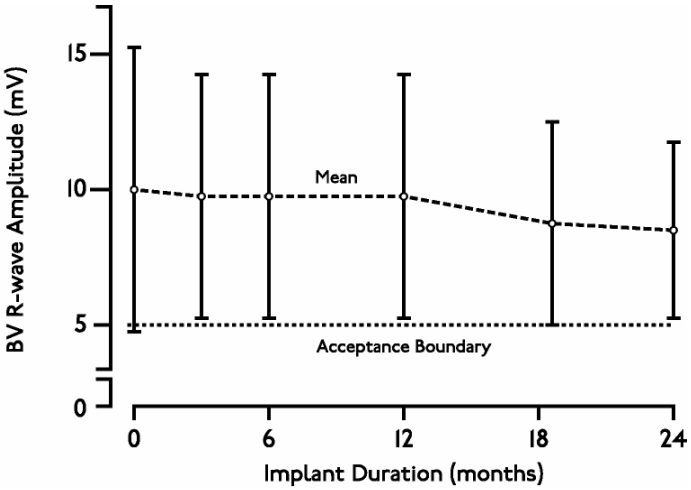
Statistic	Implant	3 Months	6 Months	12 Months	18 Months	24 Months
N	435	347	330	233	103	25
Mean +/- SD	1.8 +/- 1.2	1.7 +/- 1.3	1.9 +/- 1.5	1.8 +/- 1.2	1.8 +/- 1.1	2.0 +/- 1.2
Range	0.2 - 7.5	0.2 - 7.5	0.2 - 7.5	0.4 - 7.5	0.6 - 7.5	0.6 - 5.0
Upper Tolerance Limit	3.8	3.8	4.3	3.8	3.7	3.9

* EASYTRAK lead models: 4511, 4512, and 4513

It was hypothesized that the upper tolerance limit of the chronic left ventricular pacing threshold of the EASYTRAK lead be less than 5.5 V to ensure that an adequate safety margin exists. Chronic left ventricular pacing thresholds shown in Figure 7 are within this limit.

Figure 8: EASYTRAK Biventricular Sensed R-wave Amplitude

All patients implanted with an EASYTRAK lead at first implant, N=443

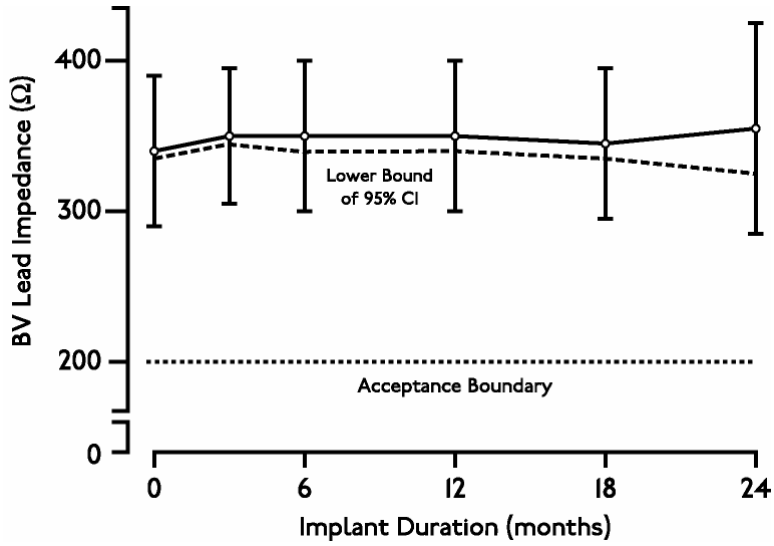


Statistic	Implant	3 Months	6 Months	12 Months	18 Months	24 Months
N	433	346	326	220	99	23
Mean +/- SD	10.0 +/- 5.2	9.9 +/- 4.4	9.9 +/- 4.5	9.8 +/- 4.4	8.9 +/- 3.5	8.5 +/- 3.3
Range	1.9 - 25.0	1.4 - 25.0	1.7 - 25.0	1.2 - 25.0	2.6 - 20.4	2.2 - 13.6

Mean chronic biventricular R-wave amplitudes are measured as a combination of the R-waves from both the right ventricle (commercially available ENDOTAK lead) and the left ventricle (EASYTRAK lead). It was hypothesized that the mean biventricular R-wave amplitude be greater than 5 mV to ensure proper sensing (Figure 8). The performance of the EASYTRAK lead system was significantly above this value ($p<0.01$).

Figure 9: EASYTRAK Biventricular Pacing Impedance

All patients implanted with an EASYTRAK lead at first implant, N=443



Statistic	Implant	3 Months	6 Months	12 Months	18 Months	24 Months
N	436	355	336	237	107	26
Mean +/- SD	340 +/- 46	352 +/- 47	349 +/- 50	351 +/- 51	347 +/- 46	356 +/- 67
Range	243 - 550	248 - 519	186 - 534	237 - 513	254 - 507	267 - 520
95% CI	(336, 344)	(347, 357)	(344, 355)	(345, 358)	(338, 356)	(329, 383)

The impedance measured by the CONTAK CD CRT-D device is the parallel combination of the left ventricular (EASYTRAK) and right ventricular (ENDOTAK) leads simultaneously. Therefore, the biventricular lead impedance will be substantially less than that of either lead alone. It was hypothesized that the lower limit of the 95% confidence interval of the mean chronic biventricular lead impedance would be greater than 200 Ω to ensure proper pulse generator function. The lower limit of the 95% confidence interval of the chronic biventricular lead impedance exceeds this value (Figure 9).

10.1.6.4.2 EASYTRAK Lead Placement Success Rate

The EASYTRAK lead was implanted in 448/517 (87%) of patients who underwent the implant procedure. Table 20 shows the reasons for inability to place the EASYTRAK lead. Table 21 provides the EASYTRAK lead implant success rate.

Table 20: Reasons for unsuccessful EASYTRAK Lead implant

Patients with unsuccessful attempt to implant EASYTRAK lead (N=69)

Reason	# of pts	%
Inability to locate or cannulate the coronary sinus	29	42.0
Dislodgment of EASYTRAK lead while removing guide catheter	13	18.8
Inability to advance the lead to a stable position	11	15.9
Inability to obtain adequate pacing thresholds	6	8.7
Procedure stopped due to coronary sinus dissection or perforation	5	7.2
Procedure stopped due to transient AV block	1	1.4
Procedure stopped due to venous perforation during subclavian stick	1	1.4
Reason not stated	1	1.4
Extracardiac stimulation	1	1.4
Inability to place an atrial pace/sense lead	1	1.4
Total	69	100%

Table 21: EASYTRAK Lead Placement Success Rate

All patients implanted or attempted with EASYTRAK lead (N=517)

Measurement	All Procedures
Number of patients implanted or attempted	517
Number of placements* of the EASYTRAK Lead	448
Rate	87%
95% CI	(84%, 90%)

* Defined as an EASYTRAK implant procedure that is concluded with the implant of the investigational cardiac resynchronization system.

Although some situations such as patient anatomy and poor thresholds cannot be avoided, increased investigator experience with the EASYTRAK lead and accessories was associated with improved success, decreased total procedure time (measured skin-to-skin), and decreased fluoroscopy exposure time (Figure 10).

Figure 10: EASYTRAK Success Rate, Procedure Time, Fluoroscopy Exposure Time

10.1.6.4.3 Biventricular Antitachycardia Pacing (ATP) Conversion Efficacy Performance

The conversion rate of induced monomorphic ventricular tachycardia (MVT) was 64% and that of spontaneous MVT was 88%.

10.1.6.4.4 Ventricular Tachyarrhythmia Detection Time

The VENTAK CHF AICD and CONTAK CD CRT-D devices sense events from both ventricles simultaneously. Ventricular tachyarrhythmia detection time was analyzed to determine if the additional lead had an adverse effect on sensing VT/VF. Guidant's ICDs typically have a detection time of two seconds. The VF detection time of 2.1 ± 0.6 seconds was statistically significantly lower than 6 seconds[1] ($p<0.01$), demonstrating that there was no statistically significant prolongation of induced VF detection times with the additional left ventricular lead. There were also no adverse events reported in which a VENTAK CHF AICD or CONTAK CD CRT-D device failed to detect a spontaneous ventricular tachyarrhythmia.

[1] Detection time at implant with legally marketed Guidant ICD devices is typically two seconds and investigators have stated that an additional delay of 3 to 5 seconds would be a clinically significant event. The expected detection time is 2 seconds [95% CI: (0, 6 sec)].

10.1.6.5 EASYTRAK LEAD AND SYSTEM SAFETY

10.1.6.5.1 EASYTRAK Lead Safety

Safety was established using the rate of adverse events that are either related to the EASYTRAK lead or to the implant procedure necessary to place the EASYTRAK lead.

An EASYTRAK lead implant procedure was performed in 517 patients with 448 patients (86.7%) being successfully implanted with the EASYTRAK lead.[2] The upper boundary of the 95% confidence interval was hypothesized to be less than 23% at six months (Table 22).

Table 22: Lead Related Adverse Events at Six Months

Patient Population	N	Event Rate (%)	95% Confidence Interval
All Patients	517	12.2	[9.4, 15.0]
NYHA Class III/IV	201	17.4	[12.7, 22.7]

Fifty-three lead-related adverse events were reported during the clinical investigation of the EASYTRAK lead among the 448 patients who were implanted with an EASYTRAK lead. Twenty-seven procedure-related adverse events were reported among the 517 patients who underwent the implant procedure for an EASYTRAK lead. The overall lead-related adverse event rate was 14.5% [95% CI (11.5–17.5%)]. Table 23 reports lead-related adverse events observed during the CONTAK CD Study.

Table 23: EASYTRAK Lead-Related Adverse Events throughout the Study

All patients implanted (N=448) All patients attempted (N=517)

Adverse Events	Total	% of pts (95% CI)
Lead-Related, N = 448		
Loss of capture/lead dislodgment	31[a]	6.9 (4.6–9.3)
Ventricular oversensing	11	2.5 (1.0–3.9)
Extracardiac stimulation	9	2.0 (0.7–3.3)
Insulation breach	2	0.4 (0.0–1.1)
Procedure-Related, N = 517		
Transient AV block	6	1.2 (0.2–2.1)
Coronary venous dissection	5	1.0 (0.1–1.8)
Coronary venous perforation	5	1.0 (0.1–1.8)
Transient renal failure	5	1.0 (0.1–1.8)

[2] For purposes of defining event rates, a denominator of 448 will be used for those adverse events that pertain to chronically implanted EASYTRAK leads and a denominator of 517 will be used for those adverse events that pertain to the implant procedure of the EASYTRA K lead.

Adverse Events	Total	% of pts (95% CI)
Pericardial effusion	2	0.4 (0.0–0.9)
Finishing wire left in lead	1	0.2 (0.0–0.6)
Right ventricular lead dislodgment	1	0.2 (0.0–0.6)
Guide wire fracture	1	0.2 (0.0–0.6)
Hypotension due to blood loss	1	0.2 (0.0–0.6)
Total (unique patients)	75	14.5(11.5–17.5)

a. Twenty-six events were successfully corrected in a repeat procedure

The most common of the 53 lead-related adverse events (>1% incidence) included loss of left ventricular capture (31 patients, 6.9%), ventricular oversensing (11 patients, 2.5%), and extracardiac stimulation (9 patients, 2.0%). These events were typically resolved with surgical intervention.

The most common of the 27 procedure-related adverse events (>1% incidence) included coronary venous trauma (10 patients, 2.0%), transient atrioventricular block (6 patients, 1.2%), and transient renal failure (5 patients, 1.0%). These events were typically resolved without intervention and no permanent long-term sequelae were reported.

10.1.6.5.2 Severe, Device-Related Adverse Events and Operative Mortality

Table 24: Adverse Events and Operative Mortality

All patients attempted or implanted (N=567)

Measurement	N	%	95% CI
Severe, Device-Related Adverse Events (Type I)*	7	1.2	(0.3%, 2.1%)
All-Cause Operative Mortality (<=30 Days Post Implant)	12	2.1	(0.9%, 3.3%)

*Percent is of patients with at least one event

The incidence of severe, device-related events was reported in 7 of 567 patients (1.2%); this was significantly less than the hypothesized rate of 20% ($p<0.01$) (Table 24). Table 25 reports system, device-related, severe adverse events observed during the CONTAK CD Study.

Table 25: System, device-related, severe adverse events

All patients attempted or implanted (N=567)

Adverse Event	# of pts	% of pts (95% CI)
Telemetry difficulty; device explanted	2	0.4 (0.0–0.9)
Ventricular tachycardia during CPX testing	1	0.2 (0.0–0.5)
Coronary sinus perforation	1	0.2 (0.0–0.5)

Inappropriate shock due to oversensing	1	0.2 (0.0–0.5)
Lead dislodgment	1	0.2 (0.0–0.5)
Anaphylaxis in association with use of a pulmonary artery catheter	1	0.2 (0.0–0.5)

Operative mortality, defined as death from any cause within 30 days of implant, was reported in 12 of 567 patients (2.1%) undergoing the implant procedure. The outcome is significantly less than the hypothesized rate of 9% ($p<0.01$). Table 26 reports the cause of death for operative mortality.

Table 26: Cause of Death for Operative Mortality

All patients attempted or implanted, N=567

Cause of Death	Implants N=501	Attempts N=66	Total N=567
Cardiac: Pump Failure	5	1	6
Cardiac: Arrhythmic	2	1	3
Non-Cardiac	2	0	2
Unknown	1	0	1
Total	**10**	**2**	**12**

10.1.6.5.3 System Safety Profile

Analysis of system safety was performed on the complication-free rate of device-related adverse events, regardless of whether or not they were related to the investigational device (Figure 11). Table 27 outlines the device related complications. This study used an acceptance criterion such that the lower boundary of the 95% confidence interval could not be less than 70%.

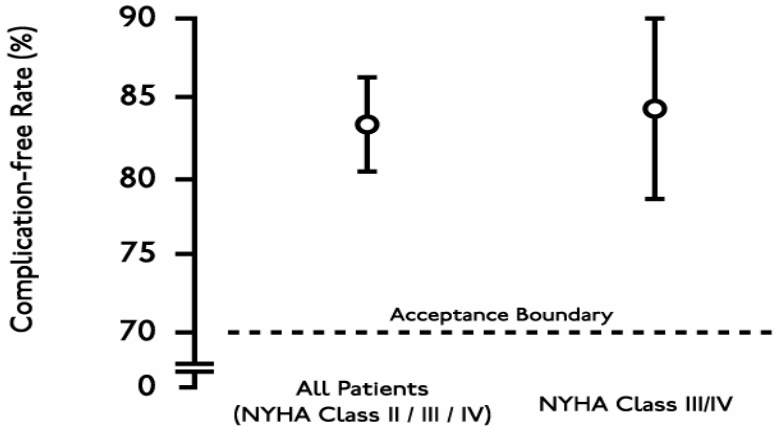
Table 27: Device-related Complications*

All patients implanted (N=448) All patients attempted (N=517)

Complication	# of pts	% of pts
All patients implanted (N=448)		
Loss of LV capture	31	6.9
Loss of right atrial capture	7	1.6
Ventricular oversensing	6	1.3
Extracardiac stimulation	5	1.1
All patients attempted or implanted (N=517)		
Infections	7	1.4

*This table represents patients attempted or implanted with the EASYTRAK lead, most common (> 1%) device-related complications reported.

Figure 11: System Safety



System safety for the All Patients group and the NYHA Class III/IV subgroup as determined by the device-related complication-free rate was within the 70% acceptance boundary for safety.

10.1.6.6 VERIFICATION OF CRT DELIVERY

The delivery of biventricular pacing throughout the CONTAK CD Study was confirmed by comparing the programmed device output to the biventricular pacing threshold and demonstrating that capture was maintained in daily activities and during exercise.

The investigational plan recommended programming the device output to at least twice the biventricular pacing voltage threshold. Electrocardiograms (ECGs) from Holter Monitors during daily activities were received and analyzed to verify that total capture was maintained at the 3-month and 6-month visits and to ensure that the safety margin was adequate. Cardiopulmonary exercise tests (CPX) were performed on patients who were randomized to receive CRT therapy at 3- and 6- month visits.

- In 623 evaluations of safety margin at baseline, three-, and six-months, the device output was programmed to deliver a voltage approximately three times that necessary to stimulate both ventricles.
- A total of 1139 Holter monitors were placed throughout the study at baseline, three- and six-months. The tests indicated only 4 instances (0.4%) of inappropriate pacing or sensing that were all corrected with device programming.
- A total of 316 CPX tests at the three- and six-month follow-up visits were performed in patients with CRT who also had interpretable ECG results. Of these, 277 (88%) had continuous CRT delivery throughout exercise. The remaining 39 patients (12%)

had continuous CRT delivery until the sinus rate exceeded the maximum tracking rate (MTR).

10.2 FOCUSED CONFIRMATORY STUDY

10.2.1 STUDY DESIGN

The Focused Confirmatory Study (FCS) was a prospective multicenter study conducted in the United States in 127 patients who participated in an exercise performance study. The purpose of the FCS was:

- To confirm effectiveness results related to functional capacity measures, specifically the Peak VO_2 and 6 minute hall walk, previously reported in the NYHA Class III/IV Subgroup of the CONTAK CD Study.

CRT was provided in the same manner for the FCS as for the CONTAK CD Study. The EASYTRAK lead, along with market approved right atrial and right ventricular leads were used to provide biventricular stimulation.

10.2.2 STUDY PATIENTS

The patients in the FCS had the same heart failure indications as the patients in the NYHA Class III/IV subgroup of the CONTAK CD Study; i.e., patient inclusion criteria included NYHA Class III or IV while on drug therapy, QRS duration ≥ 120 ms, and Left Ventricular Ejection Fraction (LVEF) ≤ 35%.

A baseline physical assessment and functional measures were performed prior to CRT system implant. Patients were eligible for participation in the study if they were capable of walking between 150 and 425m. In addition to a Six-Minute Walk test, other special tests were performed prior to implant consisting of a symptom-limited treadmill test and completion of the Minnesota Living with Heart Failure Questionnaire to assess Quality of Life. CRT therapy was enabled immediately upon device implant. Patients were followed at one week, one month, three months, six months and every three months thereafter for a routine physical assessment and device evaluation. Special testing as defined above was repeated at three months and six months post-implant.

Prior to study entry, patients were stable on optimal heart failure medications (ACE inhibitors or substitute > 1 month and beta blockers > 3 months). Patients were excluded if they were indicated for either a pacemaker or ICD or if they were hospitalized for heart failure in the month prior to enrollment.

10.2.3 BASELINE DEMOGRAPHICS

The patient characteristics at study entry are summarized in Table 28.

Table 28: Pre-implant Characteristics of Study Patients (N=127)

Characteristic	All Patients Receiving CRT	Characteristic	All Patients Receiving CRT
Age (years)	61 ± 12	QRS width (ms)	159 ± 27
Male Gender (%)	69%	LBBB/NSIVCD (%)	91%
NYHA Class III (%)	94%	Heart failure medications (%)	
Ischemic Etiology (%)	49%	• ACE inhibitor or ARB	91%
LVEF (%)	23 ± 7	• Beta blockers	77%
Resting heart rate (bpm)	73 ± 12	• Digoxin	76%
		• Diuretics	98%

10.2.4 INCLUSION CRITERIA

Inclusion criteria included:

- Moderate or severe heart failure, defined as symptomatic heart failure for at least six months with NYHA Class III or IV symptoms at the time of enrollment, AND at least one of the following events in the previous 12 months:
  - Hospitalization for heart failure management
  - Outpatient visit in which intravenous (IV) inotropes or vasoactive infusion were administered continuously for at least 4 hours
  - Emergency room visit of at least twelve hours duration in which IV heart failure medications were administered (including diuretics)
- QRS ≥ 120 ms and PR interval > 150 ms from any two leads of a 12-lead ECG
- Left ventricular ejection fraction ≤ 35%
- Left ventricular end diastolic dimension ≥ 60 mm (required only if LVEF measured by echo)
- Age ≥ 18 years
- Optimal pharmacologic therapy for heart failure
- Able to walk between 150 and 425m in a six minute walk test

10.2.5 MAJOR DIFFERENCES BETWEEN CONTAK CD CRT-D AND FOCUSED CONFIRMATORY STUDY PATIENTS

Some of the major differences between the study populations included:

- Patients were excluded from the FCS if they were indicated for either a pacemaker or implantable cardioverter defibrillator (ICD). Patients in the CONTAK CD Study were excluded if they met the indications for a pacemaker; however, they were required to meet the general indications for an ICD.
- Patients were excluded from the FCS if they were hospitalized for heart failure in the month prior to enrollment, whereas, there was no exclusion for hospitalization for heart failure in the month prior to enrollment for the CONTAK CD CRT-D patients.
- Patients in the FCS must have been on stable, optimal heart failure medications, including beta blocker therapy for three months, prior to study entry. Patients in the CONTAK CD Study could be optimized on drug therapy between the time from device implant until the treatment phase (either CRT or no-CRT) began.
- Patients in the FCS had baseline measurements performed prior to implant. Patients in the CONTAK CD Study had baseline measurements performed post-implant, but before programming of the randomized therapy.
- 77% (N=127) of patients in the FCS were on beta blockers compared to 42% (N=227) in the CONTAK CD Study.
- 49% (N=127) of the patients in the FCS had ischemic etiology compared to 68% (N=227) in the CONTAK CD Study.

10.2.6 ENDPOINTS

The primary endpoints of the study were peak VO_2 and six minute walk distance. The study was designed to show a mean change in peak VO_2 of at least 1 ml/kg/min and a 95% lower confidence bound (LCB) at least 0.5 ml/kg/min. The study was also designed to detect a statistically significant improvement in the Six Minute Walk Distance at a one-sided significance level of 0.10. Additionally, two ancillary analyses of Quality of Life Score and NYHA Class had to demonstrate a change that was directionally favorable towards CRT using descriptive statistics.

10.2.7 STUDY RESULTS

Peak VO_2

A statistically significant improvement from baseline of 0.94 ± 0.30 ml/kg/min with a 95% LCB of 0.45 was observed in peak VO_2 after six months of CRT.

Six-Minute walk Distance

Statistically significant improvements versus baseline were observed in Six-Minute Walk Distance after six months of CRT with an observed mean improvement of 50.9 ± 10.4 m. with a 95% LCB of 37.6 m.

Quality of Life

Consistent with the other analyses, a statistically significant improvement of 23.9 ± 2.6 points was observed in the Quality of Life score after six months of CRT with a 95% LCB of 19.7points.

New York Heart Association Class

After six months of CRT, a statistically significant improvement in NYHA class was observed with 60.4% of patients improving one or more NYHA class.

10.3 CONCLUSIONS DRAWN FROM THE STUDIES

10.3.1 SAFETY

The CONTAK CD CRT-D System and the EASYTRAK lead met the primary and secondary safety endpoints. Results were within protocol specified performance criteria for the rate of severe device related adverse events, antitachycardia pacing (ATP) conversion efficacy, ventricular tachyarrhythmia detection time, rate of lead related adverse events, and operative mortality. The lead placement success rate also met specified performance criteria.

In addition, analysis of the CONTAK CD CRT-D System and EASYTRAK lead safety was performed on the complication-free rate of device-related adverse events. The system was found to be within the acceptance boundary for safety.

There was no difference in the mortality or the number of hospitalizations between the treatment and control group.

10.3.2 EFFECTIVENESS

The initial CONTAK CD Study did not fully establish effectiveness of cardiac resynchronization therapy for the treatment of heart failure. A subgroup of patients with Class III/IV heart failure were observed to perform better on functional tests including Peak VO2 and Six-Minute Hall Walk. The results of the Focused Confirmatory Study were used to establish a reasonable assurance of effectiveness for cardiac resynchronization therapy in that group of patients using specific functional endpoints. Additionally, supporting evidence, such as echocardiographic measurements, which showed reductions in left ventricular intracavitary dimensions and an improvement in left ventricular ejection fraction for patients randomized to CRT for six months were used to demonstrate effectiveness.

The EASYTRAK lead met both the primary and secondary effectiveness objectives. Results were within protocol specified performance criteria for the following: chronic left ventricular pacing thresholds, chronic biventricular lead impedances, and chronic biventricular R-wave amplitudes.

11 PANEL RECOMMENDATION

The Circulatory Systems Devices Panel met on July 10, 2001 and voted not approvable (5-2), based mainly on the lack of sufficient evidence of effectiveness in the patient population studied in the CONTAK CD Study. The Panel concluded that there were no notable safety concerns with the device but that additional CRT effectiveness data was the single outstanding item needed to bring the CONTAK CD CRT-D System & EASYTRAK lead PMA to an approvable status.

12 CDRH DECISION

FDA agreed with the panel that additional information was needed to determine the effectiveness of the device. The Focused Confirmatory Study was submitted by Guidant to meet this requirement. In that study, the sponsor was able to adequately replicate the functional effectiveness results seen in the Class III/IV subgroup from the original study. Combining the results of both studies together, the sponsor has established a reasonable level of effectiveness for the CRT portion of this device in the treatment of heart failure in the defined population. The results from the original CONTAK CD study were sufficient to support the safety of the system as a whole and the effectiveness of the ICD portion of the device.

In addition, the conditions of approval include a 3-year evaluation of mortality and chronic lead performance and adverse clinical events on 1,000 patients to assess the long-term safety of the device. Physicians will also be required to undergo training by the sponsor prior to implanting the system.

On April 29, 2002 the sponsor's manufacturing facility was inspected and found to be in compliance with the Quality System Regulations (21 CFR 820).

FDA issued an approval order for P010012 on May 02, 2002. This decision was based on the entire results of the original CONTAK CD Study and the Focused Confirmatory Study.

13 APPROVAL SPECIFICATIONS

Directions for Use:	**See labeling**
Hazards to Health from Use of the Device:	**See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the Labeling**
Post-approval Requirements, Restrictions:	**See approval order.**